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A longitudinal study of resolution of allergy to well-cooked and uncooked egg

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Summary

Background Egg allergy is common and although resolution to uncooked egg has been demonstrated, there is lack of evidence to guide reintroduction of well-cooked egg.

Objectives To examine the rate of resolution to well-cooked, compared with uncooked egg in children, and safety of egg challenges.

Method A longitudinal study of egg-allergic children from 2004 to 2010, who underwent challenge with well-cooked and if negative, uncooked egg. Participants underwent repeat annual challenges and egg-specific IgE measurement.

Results One hundred and eighty-one open egg challenges were performed in 95 children whose median age of allergy onset was 12 months. Fifty-three of 95 (56%) had at least one annual repeat challenge. Pre-study historical reactions occurred to baked egg in five (5%), lightly cooked in 58 (61%) and uncooked in nine (9%); respiratory reactions occurred in 11 (12%) and seven (7%) had anaphylaxis; adrenaline was used during five reactions. There were 77 well-cooked and 104 uncooked egg challenges. Tolerance was gained twice as rapidly to well-cooked than uncooked egg (median 5.6 vs. 10.3 years; $P < 0.0001$) and continued to 13 years; hazard ratio 2.23 (95% confidence interval 1.6–3.9). Nearly 1/3 had resolved allergy to well-cooked egg at 3 years and 2/3 at 6 years. Of 28/77 (37%) positive well-cooked egg challenges, 65% had cutaneous symptoms, 68% gastrointestinal and 39% rhinitis, with no other respiratory reactions. Adrenaline was not required.

Conclusions and Clinical Relevance Resolution of egg allergy takes place over many years, with children outgrowing allergy to well-cooked egg approximately twice as quickly as they outgrow allergy to uncooked egg. There were no severe reactions to well-cooked egg challenge, and adrenaline was not required. Our data support initiation of home reintroduction of well-cooked egg from 2 to 3 years of age in children with previous mild reactions and no asthma. Resolution continues to occur in older children, so that despite an earlier positive challenge, attempts at reintroduction should be continued.

Keywords adrenaline, anaphylaxis, atopy, egg allergy, food

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Introduction

The prevalence of egg allergy in the population has been estimated at 1–2% [1–3]. Egg allergy usually develops in children with a history of atopic eczema or other food allergy (e.g. to cow's milk), but is also important as a marker of progression of the allergic march with affected children being at greater risk of sensitization to aeroallergens and asthma later in life [4].

Egg allergy is considered to resolve relatively quickly during early childhood [5] in comparison with other food

allergies such as to peanut or nuts [6]. One longitudinal study estimated that 50% of children lose reactivity to uncooked egg by 35 months [7]. However, there is a wide variation in the speed of resolution between individuals. Allergy to cooked egg resolves earlier than allergy to uncooked egg in individuals [8, 9]. Families find it useful to define when well-cooked egg allergy resolves as this can result in considerable relaxation of avoidance measures. The recently published British Society of Allergy and Clinical Immunology's (BSACI) guidelines on the management of egg allergy made the following recommendations about

reintroduction of egg: children who have had only mild symptoms (only cutaneous symptoms) on significant exposure (e.g. a mouthful of scrambled eggs) with no ongoing asthma may have well-cooked egg (e.g. sponge cake) introduced from the age of about 2–3 years at home. If this is tolerated then reintroduction of lightly cooked egg (e.g. scrambled) may be attempted from about 3–4 years [10]. These recommendations were based on limited data, clinical experience and expert opinion. Data are lacking to guide clinicians when to advise reintroduction of well-cooked egg. The outcome variable in most studies has been the resolution of allergy to uncooked egg where factors predictive of resolution (such as egg white IgE, age at diagnosis, skin prick test (SPT) weal size, including end-point titration and severity of reactions) have been identified [7, 11–13].

This study was designed to follow egg allergic children prospectively and we performed serial well-cooked and uncooked egg challenges to define the stages of resolution.

Method

Study populations

This was a longitudinal study performed at the Clinical Research Facility at the Cambridge Biomedical Research Campus between 2004 and 2010. Permission was granted by the Local Research Ethics Committee. Children were recruited to the study from the Addenbrooke's Allergy clinic and by advertisement in a national patient support group newsletter (the Anaphylaxis Campaign). Children with a history of a typical type-1 hypersensitivity reaction to egg and/or skin prick weal diameter ≥ 3 mm to whole egg extract (ALK-Abello, Horsholm, Denmark), and/or serum egg-white-specific IgE ≥ 0.35 kU/L (ImmunoCap FEIA, Phadia, Uppsala, Sweden) at the time of diagnosis were invited to participate. Subjects who had never eaten egg were enrolled if they had a positive challenge to egg and a positive SPT and/or serum-specific egg IgE.

Challenges

Open challenges were either to well-cooked (sponge cake baked at 180 °C for 20 min), or uncooked egg (uncooked pasteurized frozen whole egg nuggets, Noble Foods Ltd, Tring, Hertfordshire, UK). Five incremental doses of well-cooked (0.4 g, 0.8 g, 1.5 g, 3 g, 6 g = cumulative dose approximately 1.0 g protein) or uncooked egg (0.5 g, 1 g, 2 g, 6 g, 12 g = cumulative dose approximately 2.6 g protein) were ingested at 10-min intervals. Practical considerations such as dose acceptability resulted in different amounts of egg protein being delivered in the well-cooked and uncooked challenges. Subjects were then observed for 2 h. Each challenge was stopped after all doses were tolerated or an objective reaction occurred (i.e. development of two or more instances of erythema, urticaria

distant to the mouth or angioedema, rhinoconjunctivitis, wheeze, abdominal pain with behavioural change or vomiting, occurring within 2 h). Subjective symptoms were not counted. The subject was deemed to be tolerant if they had no reaction to ingestion of a full-dose series and if there was no report of a reaction on subsequent reintroduction at home. If a subject had tolerated well-cooked egg previously then an uncooked egg challenge was undertaken on a separate day. All other subjects underwent a well-cooked egg challenge initially, and if they passed went on to an uncooked egg challenge. Mild reactions were treated with oral antihistamines, mild airway symptoms were treated with nebulized salbutamol and adrenaline was available in case of severe reactions.

Longitudinal follow-up

Participants were followed up longitudinally and underwent annual egg challenges, SPTs and serum egg-specific IgE measurements. Subjects who reacted to the well-cooked or uncooked challenges had repeat challenges every 12 months to the same form of egg. Either full or partial resolution was recorded if subjects had no reaction to uncooked or well-cooked egg challenge, respectively. Participants who tolerated a well-cooked egg challenge were encouraged to introduce well-cooked egg into their diet. Participants who tolerated an uncooked egg challenge at their first study visit were not re-challenged.

Statistics

Summary data of non-parametric distributions are presented as medians (IQR). Medians of non-parametric data sets were compared with Mann–Whitney *U*-test. Means of normally distributed data were compared with Student's *t*-test. Comparison between multiple non-parametric data sets were made with Kruskal–Wallis test and Dunn's post-test comparison. Wilcoxon's ranked-pairs test was applied to paired non-parametric data. Data were analysed using Graphpad Prism (v5.0, San Diego, CA, USA). The rate of acquisition of tolerance to well-cooked and uncooked egg was analysed using Kaplan–Meier survival curves with log-rank test for significance and hazard ratios [and 95% confidence intervals (CI)] are presented for differences between curves.

Results

There were 181 hen's egg challenges (77 to well-cooked egg in 58 children and 104 to uncooked egg in 74 children) over a 6-year period. Ninety-five children were studied overall as several had more than one challenge during this time. Of 95 children, 42 (44%) had a single challenge, 33 (35%) had two, 12 (13%) had three, five had four and three subjects had five challenges each.

Clinical characteristics of participants

The age of onset of egg allergy (defined as first clinical reaction to egg) was median 12 months (IQR 8–13 months). There was no significant difference in the age of onset of allergy between subjects undergoing well-cooked or uncooked egg challenge. Median age at enrollment was 55 months (IQR 32–87 months). The median duration of egg allergy (first reported reaction until enrollment was 52 months (IQR 31–77 months). Male : female ratio was 1.56.

The egg causing the original historical reaction was well cooked (typically cake or biscuit) in five (5%), lightly cooked (typically scrambled eggs) in 58 (61%) and uncooked (e.g. mayonnaise) in nine (9%). Five subjects (5%) reacted to only skin contact to raw egg and 15 (16%) had never knowingly eaten or reacted to egg, but the diagnosis had been suggested by allergy testing and was confirmed by positive challenge.

The symptoms reported during each subject's worst pre-study reaction were cutaneous only in 57 (60%), gastrointestinal in 20 (21%), respiratory in 11 (12%) and seven (7%) had anaphylaxis. Of subjects who had anaphylaxis, five reacted to lightly cooked egg, one to ingestion of uncooked egg and one was unknown. Adrenaline was used in five subjects, antihistamines alone in 17, inhaled bronchodilators in two and oral corticosteroids in one. There was no information provided about treatment for 70 subjects.

Egg challenges were performed for the study at median age of 55 months (16–288 months) for well-cooked egg and median 66 months (17–184 months) for uncooked egg ($P=0.009$ for difference between medians; Mann–Whitney U -test). Overall, 28/77 (37%) of well-cooked egg and 61/104 (59%) of uncooked egg challenges were positive. There were 40 subjects whose initial challenge was to

uncooked egg because of a history of tolerance to cooked egg (21 of these challenges were negative and 19 were positive).

Symptoms elicited during positive challenges

The symptoms experienced during challenges are shown in Table 1a the treatment administered is shown in Table 1b. For well-cooked challenges, 3/28 (11%) reacted to the first oral dose (all oral itching). In 23/61 (38%) of uncooked egg challenges the subject reacted to the first oral dose (oral itching in 10, nausea in one and cutaneous rash in 12).

Immunological characteristics

The median (and IQR) SPT weal size (mm) and egg white serum IgE (kU/L) at the time of challenge for all participants were 4 mm (2–5) and 2 kU/L (0.6–6.8), respectively. Immunological parameters recorded at the time of positive and negative challenges are shown in Table 2.

Resolution

The rate of acquisition of tolerance to well-cooked and uncooked egg was analysed using Kaplan–Meier survival curves (Fig. 1 and Table 3). Tolerance was gained more rapidly to well-cooked rather than to uncooked egg (log-rank test $P<0.0001$). The median age at which tolerance occurred was 67 months (5.6 years) for well-cooked and 127 months for uncooked egg. The hazard ratio was 2.23 (95% CI (10.3 years) 1.6–3.9), indicating the rate of resolution of allergy to well-cooked egg was approximately twice that of uncooked egg.

Table 1a. Symptoms experienced during positive egg challenges (numbers of subjects are shown with percentages in parentheses). Symptoms are shown according to type of egg challenge

Type of egg challenge	Total positive challenges	Cutaneous	Gastrointestinal	Respiratory*	Rhinitis
Well cooked	28	18 (65)	19 (68)	0	11 (39)
Uncooked	61	46 (75)	34 (56)	9 (15)	20 (36)
Total	89	64	53	9	31

*Excluding rhinitis.

Cutaneous symptoms were recorded if erythema, urticaria or cutaneous angioedema occurred. Gastrointestinal symptoms were recorded if nausea, vomiting or abdominal pain (sufficient to alter behaviour) occurred and respiratory symptoms were recorded if wheezing or cough occurred during challenge.

Table 1b. Medication used during positive egg challenges (numbers of subjects are shown with percentages in parentheses). Treatment was administered by research staff and is shown according to type of egg challenge

Type of egg challenge	Total positive challenges	Oral antihistamines	Oral corticosteroids	Nebulized bronchodilator	Intramuscular adrenaline	No treatment
Well cooked	28	19 (68)	0	0	0	9 (32)
Uncooked	61	48 (79)	1	3 (5)	0	21 (33)
Total	89	67	1	3	0	30

Table 2. Skin prick test weal diameter and egg white specific serum IgE median (and IQR) at the time of egg challenges. Results are presented according to type of challenge food and outcome

Challenge food Outcome	Well-cooked egg		Uncooked egg	
	Positive	Negative	Positive	Negative
Skin prick test weal diameter (mm)	6 (4–7.5)	4 (3–5)	4 (2.5–5)	0 (0–3)
Egg white serum IgE (kU/L)	5.1 (2.6–16.6)	2.2 (0.7–7.7)	2.6 (0.7–11.5)	0.6 (0.4–1.5)

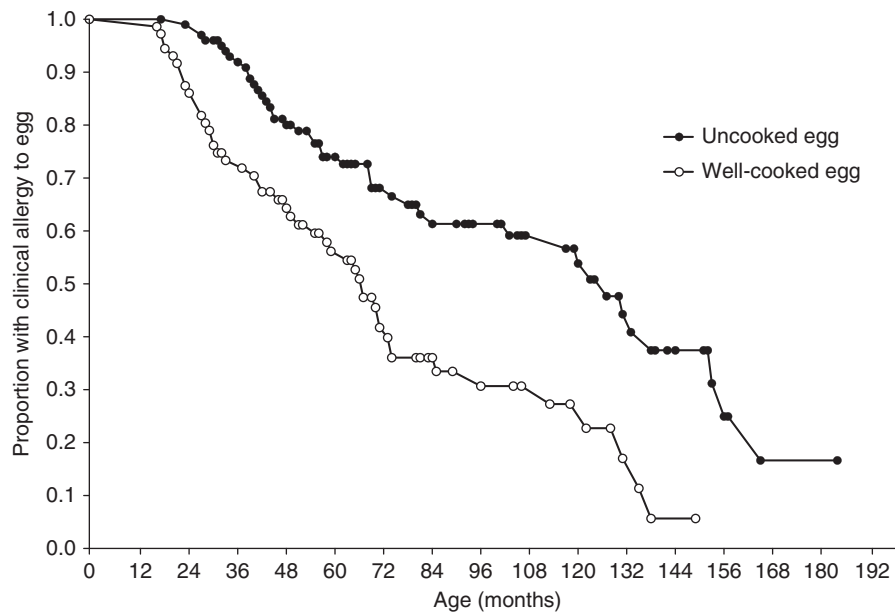


Fig. 1. Cumulative persistence (survival) of allergy to well-cooked and uncooked egg expressed using Kaplan–Meier survival curves. Log-rank test for difference between curves; $P < 0.0001$. Median age at acquisition of tolerance is 67 months (5.6 years) for well-cooked and 127 months (10.3 years) for uncooked egg.

Table 3. Proportion of subjects with allergy to well-cooked and uncooked egg at each age presented with the number still 'at risk' of resolution at each age (months)

Age (months)	Well-cooked egg		Uncooked egg	
	Proportion with positive challenge	Number remaining at risk	Proportion with positive challenge	Number remaining at risk
12	1.00	77	1.00	104
24	0.86	62	0.99	101
36	0.73	52	0.92	89
48	0.64	42	0.80	72
60	0.56	34	0.74	57
72	0.40	22	0.68	44
84	0.36	16	0.61	35
96	0.36	12	0.61	31
108	0.31	10	0.60	25
120	0.27	7	0.54	20
132	0.17	4	0.44	14
146	0.06	2	0.38	9
158	0.06	1	0.38	4
170	0	1	0.18	3
182	0	1	0.17	1
194	0	1	0.17	1

The curves show a rapid early acquisition of tolerance to both well-cooked and uncooked egg in the majority followed by a slower rate of resolution in the remaining minority. There was an early separation in the curves. In the older and slower resolvers there was a bigger difference in the slope of the curves such that the rate of resolution to uncooked egg was even slower. Nonetheless, resolution still continued to occur to cooked egg up to the age of 158 months (13.2 years) and for uncooked egg up to 182 months (15.2 years).

Conclusions

The natural history of egg allergy is for the majority to undergo spontaneous resolution over time [5]. A recent prospective challenge study showed the median time to raw egg tolerance was 3 years and 2/3 had resolved after 5 years of follow-up [7]. In contrast we found that 3/4 had not resolved by 5 years of age and the median age at complete resolution of egg allergy was 10 years. This discrepancy may be partly explained by methodological differences, as the population we studied was older. Nonetheless, both studies underestimate the true rate of resolution because subjects were likely to have achieved tolerance to egg in advance of the egg challenge.

Families find it helpful to establish when their children have achieved tolerance to well-cooked egg, so that they no longer worry about well-cooked egg as a hidden ingredient in foods, and allergen avoidance becomes less onerous. A recent study of egg-allergic patients aged between 0.5 and 25 years showed that 70% were able to tolerate challenges with well-cooked egg [14]. After a negative challenge, well-cooked egg could be reintroduced into the diet on a regular basis, this is shown to be well tolerated with no adverse effect on growth, allergy or intestinal permeability [14]. In a previous study, the food allergy related quality of life (QOL) score improved for children who underwent food challenge in a clinic setting [15]. The improvement in QOL occurred after both positive and negative challenges, implying that all families found the challenge process helpful regardless of the outcome.

Data advising on the timing of reintroduction are scarce, recently published BSACI guidelines recommend that 'children who have had only mild symptoms (cutaneous) on significant exposure (e.g. a mouthful of scrambled eggs) with no ongoing asthma could have well-cooked egg (e.g. sponge cake) reintroduced from the age of about 2–3 years at home' [10]. In our study, tolerance to well-cooked egg was achieved approximately twice as quickly as tolerance to uncooked egg, in the same population. There is a considerable difference, with median age at tolerance of 5 and 10 years for well-cooked and uncooked egg, respectively. Our data therefore support this guideline (at 3 years 27% had no reaction to a cooked egg challenge and reactions were universally mild).

Further, nearly 2/3 had resolved allergy to well-cooked egg at 6 years. It is important to note that resolution can occur in older children, so that despite an earlier positive challenge, attempts at reintroduction should be continued. Our data support undertaking well-cooked egg challenge as this is usually tolerated even when the skin test is positive (e.g. 3–5 mm weal diameter; Table 2).

There are a number of safety factors built into this approach. The proportion of egg in the food is very small for well-cooked egg reintroduction (e.g. a cake). The age when resolution is demonstrated by challenge is likely to be greater than the age at which resolution actually occurs, therefore a higher proportion would have resolved than is apparent. Data from a different population, who were enrolled at a younger age suggest that resolution may occur even earlier [7, 16]. Our data are based on full-dose challenges of egg given over 2 h, whereas the home reintroduction recommendation is over days or weeks. Thus the dose of allergen is significantly less and the rate of reintroduction significantly lower. Lastly, for lightly cooked reintroduction, children would have already introduced well-cooked egg into their diet, therefore the process of resolution has begun. We also recommend that home-based reintroduction is not undertaken under certain circumstances (Table 4).

The safety of performing home reintroduction of well-cooked egg can be considered by examining challenge studies, although there are important methodological differences between home reintroduction and egg challenge protocols. In home reintroduction, doses are introduced slowly over a number of days and the amount of allergen is low [10]. In studies using egg challenges the dose is built up rapidly, over a few hours. The onset of reactions during a challenge is rapid, with most symptoms occurring in the first 30 min of ingestion [16]. Urticaria and/or angio-oedema occur in up to 90% of subjects (within minutes) and gastrointestinal symptoms are described in 10–44% (within 2 h) [3, 16, 17]. The majority of reactions, however, are mild. Reporting of more severe reactions with significant respiratory symptoms varies widely from 2% to 34% in challenge studies [16–21]. One study which reported a 7% rate of severe reactions

Table 4. Home-based reintroduction of egg should be avoided in the following circumstances. A hospital-based egg challenge may be appropriate but the timing of this should be considered on an individual basis (adapted from BSACI guidelines on management of egg allergy [10])

Children with previous egg allergy symptoms that affected breathing (cough, wheeze or swelling of the throat, e.g. choking), the gut (severe vomiting or diarrhoea) or the circulation (faintness, floppiness or shock)
Children who had a less severe reaction after only trace exposure
Children who have poorly controlled asthma

BSACI, British Society of Allergy and Clinical Immunology.

including 21% with respiratory reactions, but this involved administration of a whole raw egg in one dose [21]. A retrospective chart review of clinical practice challenges reported a severe reaction rate of 17%, however, the type of egg used in challenges was not reported [19]. Most of these studies used raw or lightly cooked egg challenges and/or large single doses and/or short-dose intervals. A cautious regime using sequential well-cooked then lightly cooked egg with stepwise reintroduction as suggested is better tolerated. In the present study, reactions to well-cooked egg were mild to moderate with no significant respiratory features, the majority having only cutaneous or gastrointestinal reactions. This should provide reassurance for clinicians when reintroducing well-cooked egg back into the diet of children with mild egg allergy.

A recent publication cautioned against any home introduction of well-cooked egg, after reporting that injectable adrenaline was administered to a number of children during hospital-based challenges to cooked egg [14]. However, the challenges involved a large dose of egg given over a few hours. In addition the cohort challenged contained significant numbers of children with severe egg allergy and asthma, two factors which would lead one to consider a hospital supervised challenge (see table 4).

Data from our group and others [8] show that children who tolerate well-cooked egg may still react to uncooked egg. In case series severe reactions have been reported [9]. The speed with which allergy to uncooked egg resolves varies greatly between individuals; therefore the timing and appropriateness of reintroduction should be individually assessed. Biomarkers could be helpful. Recent studies have suggested that the absolute level [12] and the rate of fall [11] of egg white IgE may help to identify patients in whom the egg allergy has resolved. Children with a peak level of egg IgE < 2 kU/L had the fastest rate of resolution [12], and a reduction in serum egg-specific IgE level of 50% over 12 months was associated with a 0.52 probability of tolerance [11]. Boyano-Martinez et al. [7] in a prospective study found that serum egg IgE of 1.98 kU/L

and skin prick weal of 6 mm could differentiate early from late resolvers to raw egg.

There has been recent interest in measuring specific IgE directed against major egg allergens, particularly ovomucoid, which is resistant to degradation by heating [8, 22]. Jarvinen et al. [23] demonstrated that IgE antibodies against sequential ovomucoid epitopes were found more often in patients with persistent rather than resolved egg allergy. A study of 108 egg allergic subjects (median age 35 months) showed that low levels of egg white and ovomucoid-specific IgE were associated with tolerance to well-cooked egg [22]. If confirmed, measurement of specific IgE directed against major allergens may help to predict resolution of egg allergy and the selection of patients for home introduction of well-cooked egg products. Guidelines for reintroduction of cooked egg [10] might be modified by data from IgE levels to component resolved allergens.

We have described the clinical features, outcomes and natural history of resolution of egg allergy in a large nationally recruited sample of young children from the United Kingdom, to aid clinical decision making. Tolerance to well-cooked egg is achieved twice as quickly as to uncooked egg; well-cooked egg challenges are well tolerated with no severe reactions. Resolution continues to occur up to about 13 years, and often occurs to well-cooked egg when there is a positive SPT. Therefore, we have provided data to support individualized home reintroduction of egg, with built in safety factors [10].

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